

BIOGRAPHICAL SKETCH

NAME OF FELLOWSHIP APPLICANT Naomi Sayre	POSITION TITLE
eRA COMMONS USER NAME SayreN	Assistant Professor/Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Rochester, Rochester NY	BA	1999-2003	Biology
Tufts University Sackler School of Graduate Biomedical Sciences, Boston MA	Ph.D.	2004-2010	Cellular and Molecular Physiology
University of Texas Health Science Center, San Antonio TX	Post-doc	2010-2015	Cell biology and neuroscience

A. Personal Statement

My research focuses on understanding the processes that contribute to successful recovery after damage to the central nervous system. My training has emphasized a variety of approaches to understand recovery processes after stroke, traumatic brain injury, and spinal cord injury-which all have common mechanisms involved in damage and recovery. Technical approaches in my laboratory include strong, *in vivo*-based protocols such as behavioral analysis, injury modeling, transgenic animals, and *in vivo* optical imaging. My laboratory is also proficient in a variety of cell biological and biochemical approaches to study astrocytes and neurons in culture. A significant focus of my research involves understanding the role of an Apolipoprotein E receptor, LDLR-related protein 1 (LRP1) in astrocyte and neural stem cell physiology. At this point in my career, I have been involved in the laboratory training and mentorship of 8 neurosurgical residents, 3 medical students, 5 undergraduate students, and 4 graduate students. My lab currently is comprised of one Ph.D. student, one Neurosurgical Resident, one undergraduate and 2 laboratory technicians within the Department of Neurosurgery. Xiangya medical students will attend weekly laboratory meetings with my laboratory and other members of the Department of Neurosurgery. They will also attend Neurosurgery Grand Rounds, Journal Club, and be given an opportunity to shadow Neurosurgeons in our department.

Positions and Honors

Positions:

06/2003-08/2004	Veterinary Technician, Charles River Laboratories, MA
11/2010-06/2015	Post-doctoral Fellow, Dept. of Cellular and Structural Biology, UT Health Science Center (UTHSCSA), San Antonio, TX
06/2015-present	Assistant Professor Research, Dept. of Neurosurgery, UTHSCSA, San Antonio TX

Academic and Professional Honors

Honors:

1999-2003	Bausch and Lomb Scholarship, University of Rochester, NY University of Rochester Dean's List
2005-2010	National Research Service Award (NRSA) Institutional Training Grant, Tufts U., MA
2007	Honorable Mention, Charlton Poster Competition Sackler Junior Division, Tufts U., MA
2008	First Place, Charlton Poster Competition, Sackler Senior Division, Tufts University, MA
2011	Graduation Speaker, Tufts Medical School Graduation, MA
2012-2013	NRSA Institutional Training Grant, UTHSCSA, TX
2012	NIH Loan Repayment Program Award, NINDS Clinical Sciences
2013	1 st place, postdoctoral poster award and selected speaker, Frontiers in Translational Science Day, UTHSCSA, TX
2013	1 st place, postdoctoral poster award, Cellular and Structural Biology Retreat
2013	Pilot Project Award in Stem Cells and Aging, Cellular and Structural Biology Dept, UTHSCSA
2013	Travel Award, Postdoctoral Research Forum, UTHSCSA, TX
2013	American Heart Association Postdoctoral Fellowship, Southwest Section
2014	Susan B. Naylor Award for Excellence in Postdoctoral Studies, Cellular and Structural Biology Dept. UTHSCSA
2014	Barbara H. Bowman Postdoctoral Research Scholar Award, UTHSCSA

Professional memberships

2011-present	Society for Neuroscience
2012-present	American Physiological Society
2013-present	American Heart Association
2013-present	American Society of Neurochemistry

B. Contribution to Science

1. As a graduate student, I showed that the liver can recover from cholesterol storage defects-Niemann Pick C is a neurodegenerative disease characterized by lysosomal storage of cholesterol and other lipids. Patients with Niemann Pick C also exhibit significant liver phenotypes, including liver cirrhosis, hepatomegaly, and steatosis. I wanted to test whether patients with significant liver disease could recover should a treatment option become available. I used antisense oligonucleotide technology to successfully knock down expression of the Niemann Pick C disease causing gene in the liver, thereby causing liver disease. Withdrawal of the oligonucleotide allowed re-expression of the Niemann Pick C disease causing gene. I found that significant recovery is possible, although liver fibrosis remains a concern. The results from this graduate research topic were published in *Journal of Lipid Research*, and the results can be extrapolated to several liver diseases, including non-alcoholic fatty liver disease, hepatitis, and cirrhosis.

Publications/abstracts relevant to this contribution:

Sayre, NL; Rimkunas, VM; Graham, MJ; Crooke, RM; Liscum, L. "Recovery from Liver Disease in a Niemann-Pick type C Mouse Model" *J. Lipid Res.* Aug;51(8):2372-83, 2010. **PMCID: PMC2903820**

Vincent, M.; **Sayre, NL**; Graham, MJ; Crooke, RM; Liscum, L. "Evaluation of an Anti-Tumor Necrosis Factor Therapeutic in a Mouse Model of Niemann-Pick C Liver Disease" *PLoS ONE*. Sep 23;5(9):e12941, 2010. **PMCID: PMC2944848**

Sayre, NL; Liscum, L. "Cholesterol trafficking and uptake in an abnormal NPC1 cell model." Abstract for Poster Presentation. *Charlton poster competition*, Boston, MA 2007 (**honorable mention**) and *Ara Parseghian meeting for NPC disease research*. Tucson, AZ. 2008.

Sayre, NL; Rimkunas, VM; Graham, MJ; Crooke RM; Liscum L. "Liver recovery in an antisense oligonucleotide knockdown of Niemann-Pick C1 in mice." Abstract for Poster Presentation. *Ara Parseghian meeting for NPC disease research*. Tucson, AZ 2009 and *Charlton poster competition*, Boston, MA 2009 (**First Prize**)

2. As a post-doc, I showed that mitochondrial isoforms of thyroid hormone receptor play a major role in the acute upregulation of ATP production after stimulation with thyroid hormone. Before thyroid hormone receptor was described as a transcription factor, several scientists discovered that thyroid hormone could rapidly (within 15 minutes) stimulate increases in ATP production independent of any genetic transcription. For over thirty years, it was not clear what mechanisms could be responsible for this quick response to thyroid hormone. Together with my co-authors, I showed that shortened, mitochondrial thyroid hormone receptors were responsible for this acute upregulation of ATP production. Moreover, I found that the rapid increase in ATP production was dependent on upregulation of fatty acid oxidation. We found evidence that the mechanism of upregulated fatty acid oxidation involved increased complex formation of the long-chain fatty acid oxidation machinery, termed hydroxyl acyl CoA dehydrogenase alpha (HADHA). The results from the research topic were published in *Molecular Endocrinology*.

Publications/abstracts relevant to this contribution:

Sayre NL*, Chocron ES*, Holstein D, Saelim N, Ibdah JA, Dong LQ, Zhu X, Cheng SY, Lechleiter JD 2012. "The Trifunctional Protein Mediates Thyroid Hormone Receptor-Dependent Stimulation of Mitochondrial Metabolism." *MolEndocrinol*. Jul;26(7):1117-28, 2012. **PMCID: PMC3385793**

Sayre, NL; Lechleiter, JD. "Thyroid Hormones Are Significant Regulators of Fatty Acid Oxidation in the Mitochondria." *Current Trends in Endocrinology*. 6:65-76, 2012. **PMCID: PMC3891511**

3. As a post-doc, I have showed that a significant component of thyroid-hormone based neuroprotection after stroke involves upregulation of astrocyte fatty acid oxidation. A natural progression of the research topic described in 2 involves understanding the mechanism by which thyroid hormone can act as a neuroprotective agent after stroke. I hypothesized that it could involve fatty acid oxidation. I have shown for the first time that astrocytes are capable of upregulating ATP production in a fatty acid oxidation dependent manner upon thyroid hormone stimulation. Moreover, I found that treatment with thyroid hormone protected astrocytes from loss of viability after oxygen glucose deprivation except for when fatty acid oxidation was inhibited. Finally, I show that inhibition of fatty acid oxidation significantly increases the lesion size after stroke. The results have just been submitted to the *Journal of Cerebral Blood Flow and Metabolism* for review.

Publications/abstracts relevant to this contribution:

Sayre, NL; Holstein, D; Sifuentes, M; Cheng, SY; Zhu, X; Lechleiter, JD. "Thyroid hormone protects against ischemic stroke induced damage by stimulating fatty acid oxidation in astrocytes." *Journal of Cerebral Blood Flow and Metabolism*. 2016. **PMID: 26873887**

Sayre, NL, Holstein D, Lechleiter JD. "Thyroid hormones stimulate astrocyte fatty acid oxidation and mitochondrial energization, increase cell survival after oxidative stress, and reduce necrosis post-ischemia in mice." Abstract for Poster Presentation. *Gordon Research Conference-- Glial Biology: Functional Interactions among Glia & Neurons*. Ventura, CA 2013.

Sayre, NL, Holstein D, Lechleiter JD. "Thyroid hormones can increase astrocyte fatty acid oxidation and survival in astrocytes; a possible mechanism for decreased tissue necrosis after cerebral stroke." Abstract for Poster Presentation. *Translational Science Research Day, UTHSCSA*. San Antonio, TX 2013(**First place**).

4. I have helped elucidate recovery in trauma models of brain injury. I developed a mouse model of repetitive traumatic brain injury that shows significant deficits in the long term after injury, and also found that stimulation of astrocyte mitochondrial metabolism soon after injury prevents those long term deficits. A significant health concern to veterans of war and athletes is the fact that repetitive traumatic brain injury significantly increases the likelihood that patients will develop neurological deficits with aging. Exactly why this is so is not well characterized, especially because animal models that recapitulate the phenotypes in humans has been lacking. I subjected mice to repetitive traumatic brain injury and allowed them to age for up to a year and a half, and have found that mice display social abnormalities and hyperactivity in response to novel situations. Moreover, I found that purinergic-mediated stimulation of astrocyte metabolism prevents most of the age-associated deficits associated with repetitive traumatic brain injury.

Publications/abstracts relevant to this contribution:

Sayre, NL; Chen, Y; Sifuentes, M; Stoveken, BJ; Lechleiter, JD. "Purinergic Receptor Stimulation Decreases Ischemic Brain Damage By Energizing Astrocyte Mitochondria." in Glutamate and ATP at the interface of Metabolism and Signaling in the Brain. Adv Neurobio. 2014. **PMID 25236727.**

Glober, NK; Fletcher, LM; Sprague, S; Digicaylioglu, M; Jimenez, D; **Sayre, NL.** "The Regulation of Aquaporin 4 is Altered After Oxygen Glucose Deprivation: Implications for Treatment of Traumatic Brain Injury." PlosOne, *in revision.* 2016.

Sayre, NL; Sprague, S; Stoveken, BJ; Digicaylioglu, MD; Lechleiter, JD. "The Long-Term Impact of Treating Astrocytes After Repetitive Traumatic Brain Injury." Abstract for Poster Presentation. *American Society for Neurochemistry.* Long Beach, CA 2014.

D. Research Support:

Current Support:

Veteran's Administration Career Development Award (CDA-2)

The influence of ApoE4 on signaling and poor outcome after traumatic brain injury.

4/1/2017-3/31/2022

The goal of this project is to study the influence of low-density lipoprotein receptor related protein 1 on long term outcome following traumatic brain injury.

\$160,000 year 1/\$792,000 total

American Heart Association 15BGIA25090292

ApoE4 modulation of recovery and long term-complications after stroke

07/2015-06/2017

The goal of this project is to test how the low-density lipoprotein receptor related protein 1 affects stroke pathology.

\$70,000 year1/\$140,000 total

Department of Neurosurgery Start-up funds

Provided in support of a new research program.

Pending support:

Owen's Medical Foundation

The influence of LRP1 in the neural stem cell niche after stroke

The goal of this project is to test how low-density lipoprotein receptor related protein 1 affects neural stem cell proliferation, differentiation, migration after stroke, and whether altered stem cell properties affect stroke recovery.

Completed Support:

Center for Biomedical Neuroscience, UTHSCSA

Targeting astrocyte hemichannels to halt secondary spread of injury after spinal cord injury

01/2016-12/2016

The project is a pilot project to examine whether treating spinal cord injury with function blocking antibodies to connexin 43 is a viable therapeutic

American Heart Association 13POST16820029

Regulation of Glial Mitochondrial Metabolism and Neuroprotection

07/2013-06/2015

The goal of this project is to determine whether astrocyte fatty acid oxidation is a valid means to protect the brain from stroke damage.

Role: PI

NIH 2-T32-HL007446-31

Pathobiology of Occlusive Vascular Disease (PI: Linda McManus)

09/2012-08/2017

A competitive institutional training grant position.

Role: Trainee.

NIH NINDS Clinical Sciences Loan Repayment Program

Regulation of Glial Mitochondrial Metabolism and Neuroprotection

10/2012-09/2014

This award repays student loan debt over a two year period. During the repayment period, the recipient must engage in clinically-relevant research.

Role: PI

Barshop Institute of Aging and Longevity Pilot Project Grant

Does Apolipoprotein E modulate stem cell proliferation via BMP signaling?

05/2013

The goal of this project is to test whether apolipoprotein E can affect cellular signaling by interfering with the ability of low-density lipoprotein receptor related protein (LRP1) to clear plasma membrane receptors, and to generate data for a full grant proposal.

Role: PI

The influence of LRP1 in the neural stem cell niche after stroke

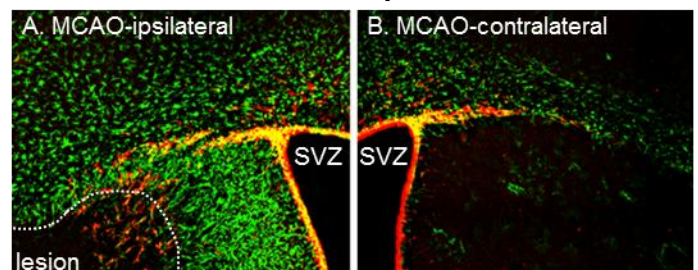
Cardiovascular disease and stroke are the top causes of death in the United States. Long-term complications due to stroke are the primary cause of long-term disability. My laboratory aims to find a better mechanistic understanding of processes that determine the ability to recover function after stroke. A Xiangya medical student in my lab will have an opportunity to study mouse models of stroke, and the role that neural stem cells (NSCs) play in recovery processes. In addition to performing basic science studies on stroke models, we aim to provide a medical student with an enriched training environment that improves their skills as a physician-scientist. This will include close one-on-one mentoring with the PI, review of journal articles, attendance at seminars, and honing of scientific writing and presentation skills. Students will also have an opportunity to interact with and shadow neurological surgeons in our home department, the Department of Neurosurgery, in order to better understand the translational impact of our research.

Description of project

The neural stem cell (NSC) niche maintains pools of NSCs which provide neural progenitors during normal brain development and aging. Brain ischemia stimulates NSC proliferation, along with production of neuroblasts and pro-reparative glia which migrate from the site of injury where a limited number of these neuroblasts differentiate and integrate into the existing circuitry¹⁻³, while others serve as neurotrophic factories that protect existing cells from injury and death⁴. The importance of this NSC response has not been fully elucidated, but we do know that limiting the ability of NSCs to respond increases lesion size and worsens behavioral outcomes^{1,3,5-9}. **The goal of this project is to test the influence of the low density lipoprotein related protein 1 (LRP1) on the activation of NSCs, particularly after stroke.**

Significance: LRP1 is a plasma membrane receptor which binds to a variety of extracellular ligands and other plasma membrane proteins¹⁰. The net result of this promiscuous binding is that LRP1 undergoes receptor mediated endocytosis to clear proteins from the extracellular milieu. Therefore, disruption of LRP1 function has the potential to cause altered response to signaling factors in the NSC niche. Remarkably, despite its fundamental role in modulation of signaling, *LRP1 in NSC biology is virtually unstudied*. Total knock-out of LRP1 is embryonic lethal¹⁰, and so it clearly plays some role in cellular development from stem cells. **We hypothesize that the clearance of signaling molecules on NSCs by LRP1 determines NSC response to stroke.** We expect that studying the role of LRP1 in NSC biology and stroke will contribute both to the basic understanding of LRP1 in NSC biology, but also to the understanding of NSC biology in stroke.

Innovation: We recently bred a new strain of mice which will allow us to inducibly knock out LRP1 specifically within nestin-expressing NSCs in adult mice. In addition to lacking LRP1, these mice express a red-fluorescent protein (td-tomato). When induced using tamoxifen, recombination causes both a knockout of LRP1 and induced expression of td-tomato specifically within NSCs. This powerful new mouse model will enable us to track the fate of NSCs *in vivo* as they proliferate or migrate. Similarly, we can isolate these NSCs and perform *in vitro* experiments which allow us to mechanistically understand differences in NSC biology. We will use this mouse model to test how loss of LRP1 affects NSC function using a combination of *in vitro* cell culture approaches as well as *in vivo* mouse models of stroke.



Middle cerebral artery occlusion (MCAO) and NSC migration. Mice expressing NSC-specific tracking protein td-tomato were subject to transient MCAO, and allowed to recover for 1 week. Shown is a histological section immunolabeled with the astrocyte marker GFAP (in green), while NSCs are red. A) Image showing lesioned brain tissue traced in white. Red NSCs have migrated into the lesion near the striatum, and glial scarring is evident. B) Image showing brain tissue on the opposite side of the brain from the stroke lesion, showing no migration of NSCs or glial scarring in the striatum.

References

- 1 Arvidsson, A., Collin, T., Kirik, D., Kokaia, Z. & Lindvall, O. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nature medicine* **8**, 963-970 (2002).
- 2 Benner, E. J. *et al.* Protective astrogenesis from the SVZ niche after injury is controlled by Notch modulator Thbs4. *Nature* **497**, 369-373, doi:10.1038/nature12069 (2013).
- 3 Thored, P. *et al.* Persistent production of neurons from adult brain stem cells during recovery after stroke. *Stem cells (Dayton, Ohio)* **24**, 739-747 (2006).
- 4 Jin, K., Wang, X., Xie, L., Mao, X. O. & Greenberg, D. A. Transgenic ablation of doublecortin-expressing cells suppresses adult neurogenesis and worsens stroke outcome in mice. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 7993-7998, doi:10.1073/pnas.1000154107 (2010).
- 5 Jin, K. *et al.* Evidence for stroke-induced neurogenesis in the human brain. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 13198-13202, doi:10.1073/pnas.0603512103 (2006).
- 6 Jin, Q. *et al.* Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke. *Brain, behavior, and immunity* **40**, 131-142, doi:10.1016/j.bbi.2014.03.003 (2014).
- 7 Ohab, J. J., Fleming, S., Blesch, A. & Carmichael, S. T. A neurovascular niche for neurogenesis after stroke. *J Neurosci* **26**, 13007-13016 (2006).
- 8 Robin, A. M. *et al.* Stromal cell-derived factor 1alpha mediates neural progenitor cell motility after focal cerebral ischemia. *J Cereb Blood Flow Metab* **26**, 125-134 (2006).
- 9 Zhang, R. L., Zhang, Z. G. & Chopp, M. Ischemic stroke and neurogenesis in the subventricular zone. *Neuropharmacology* **55**, 345-352, doi:10.1016/j.neuropharm.2008.05.027 (2008).
- 10 Lillis, A. P., Van Duyn, L. B., Murphy-Ullrich, J. E. & Strickland, D. K. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. *Physiological reviews* **88**, 887-918, doi:10.1152/physrev.00033.2007 (2008).